The Importance of Assuring Quality Throughout the Lifecycle

Richard L. Friedman, M.S.

Deputy Director, Science and Regulatory Policy

Office of Manufacturing Quality

FDA/CDER/OC

ISPE/PQRI/FDA Quality Manufacturing Meeting (June 6-8, 2016)

Agenda

- Importance of Quality Throughout the Drug Lifecycle
  - Consistent manufacturing is essential to assure each batch is safe & effective
  - Effective Quality Risk Management (QRM) supports reliable manufacturing throughout the lifecycle
- State of Control
- Quality System Oversight of Manufacturing
  - Identifying supply chain, process control, manufacturing capability and other potential lifecycle risks
  - Importance of management oversight

Importance of Quality Throughout Drug Lifecycle

Expectations for Quality

Patients and caregivers assume that their drugs:

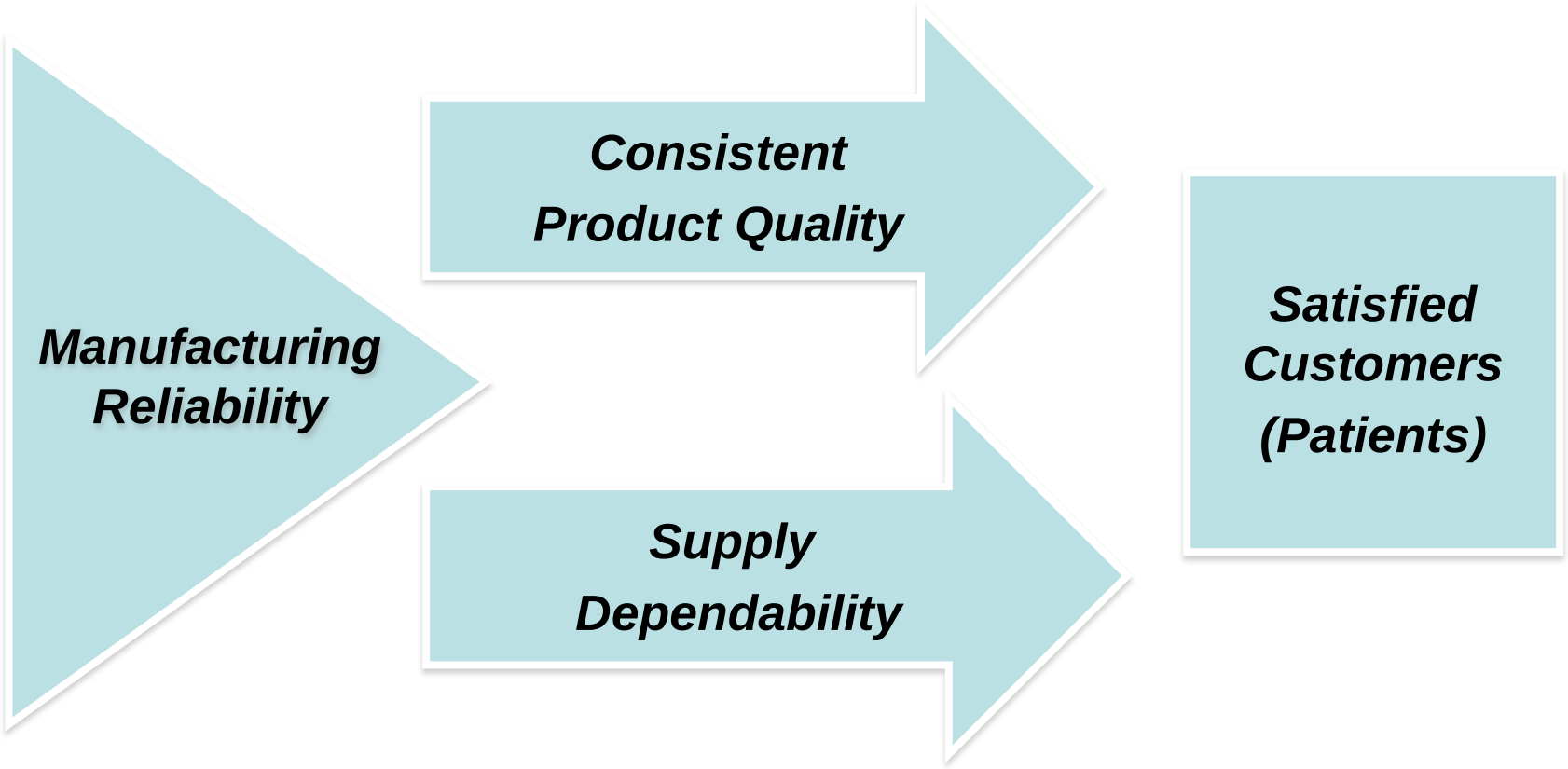
- Are safe, efficacious, and have the correct identity
- Deliver the same performance as described in the label
- Are made in a manner that ensures quality
- Perform consistently over their shelf life
- Will be available when needed

Sarah Pope, OPQ/ONDP

ICH Q9 (Quality Risk Management) Concept Paper - 2003

- **Technology Focus**
  - Increase process capability
  - Focus on critical control points
- **Product**
  - Stabilize manufacturing steps (decrease variability)
  - Guarantee shelf-life
- **People**
  - Result in behaviours that promote superior performance of the Quality System
- **Customer**
  - Reduce deviations
  - Reduce market complaint rate
  - Reduce technical-related adverse events
    - i.e., Improve Quality Performance for the Patient

Expectations for Quality (continued)



State of Control

PQRI: Process Robustness (2006)

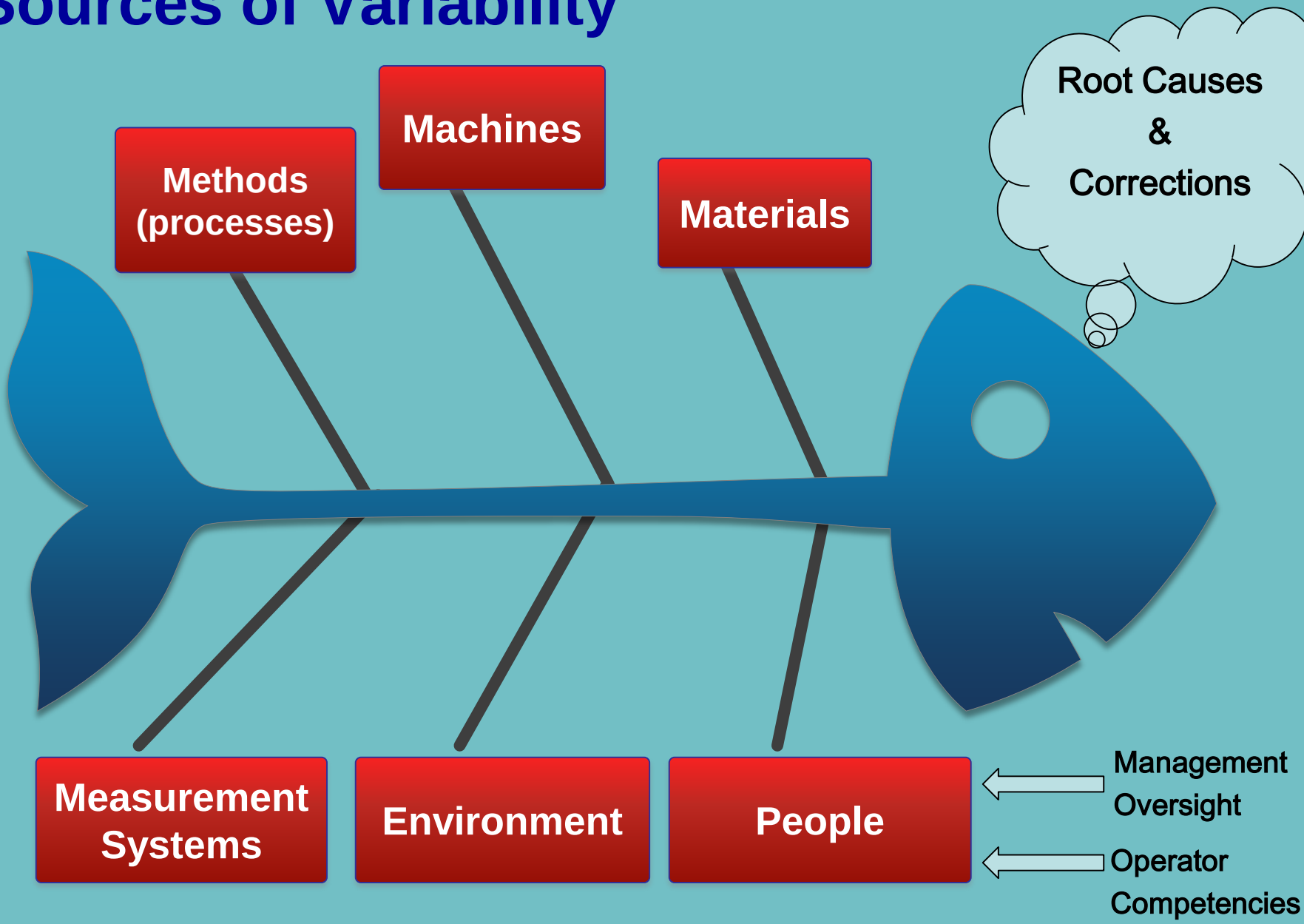
- **Capability**:
  - "**It is upon transfer to Manufacturing that assessment of the true process capability** and **robustness** as well as any process improvement or remediation will **begin…"**
- **Variation**:
  - "When the product is transitioned to Manufacturing, it will most likely encounter a **much** wider range of variation on the parameters than seen in development."
  - "For example, [drug product] attribute variability may increase due to a **wider range in incoming raw material** parameters that cannot feasibly be fully studied in R&D."

"Process Robustness- A PQRI White Paper," PharmEng, May 2006

Why Quality Matters…
Impact of Substandard Manufacturing (e.g.)

- Product (Asthma Drug) is 500% of Label Claim
- Seizure Drug: Capsules partially filled or empty
- Seizure Extended Release Drug: Poor Dissolution
- Non-sterile LVP Bags
- Non-sterile Vials
- Superpotent Narrow Therapeutic Index Tablet (Digoxin)
- Injectable Emulsion with High Pyrogens
- Antiseptic pads contaminated with gram negatives (used to wipe catheters and injection sites; presurgical)
- Microbiologically contaminated Eye Drops (used post-surgery)
- Empty Rescue Inhalers (Asthma)
- NTI Uniformity Failures (Thickness, CU)
- Transdermal dose dumping
- Label Mixups. e.g. Bottle labeled as 3mg Warfarin actually contained 10mg Warfarin (a REMS drug).
- Heparin contamination with toxic substitute
- Autoinjector does not deliver drug (epinephrine)

Sources of Variability



Quality System Oversight of Manufacturing and Quality

A Robust Quality System Assures a State of Control

The Pharmaceutical Quality System:

- **Drives Sound Lifecycle Decision-making**
  - Uses Scientific and Risk-Based Approaches
- Establishes and Maintains a **State of Process Control**
  - **Vigilantly monitors** process performance & product quality
  - Assures reliable processes and products through **management oversight** (checkpoints, escalation, executive involvement) **throughout the supply chain**
  - **Creates real "fixes" to problems** (long term, systemic)
    - Continual Improvement

Management Oversight of Manufacturing Quality

In 2012, the FDASIA legislation amended the statutory GMP Definition in the FD&C Act 501 as follows:

"For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' includes the **implementation of oversight** and controls over the manufacture of drugs to **ensure quality,** including **managing the risk** of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

"*Section 711: Enhancing the safety and quality of the drug supply*" specifies management oversight from Raw Materials to Intermediate Materials to Finished Product

Risk Management: Do you *connect the dots* in Daily Manufacturing? In your Supply Chain?

Daily Risk Management Decisions Determine Reliability of Quality and Supply

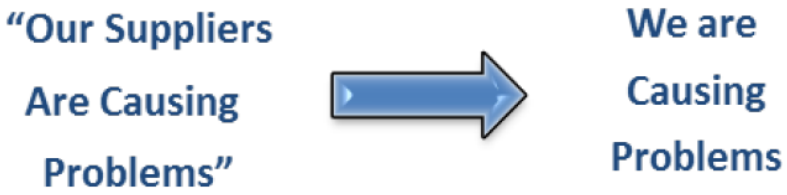
A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality. **Management's daily decisions** on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will **ultimately determine the quality** of the drugs that are shipped from a given facility.

[Woodcock, J and M. Wosinska, Clinical Pharmacology & Therapeutics, "Economic and Technological Drivers of aGeneric Sterile Injectable Drug Shortage," Jan 2013]

Supply Chain Management

Figure 1: Supply Chain Process Flow

Figure 2: Major Paradigm Shift revealed through Failure Mode Analysis



Recognition that it is a failure of the Owner's Supplier Management Program when they are ***unaware of a problem or change*** at the supplier that may affect quality (i.e., basic knowledge needed for effective quality risk management).

Xavier Good Supply Practices Concept Paper, 2015

Ongoing Supply Chain Oversight: *Selection, Qualification, Monitoring and Risk Review*

II. Poor Supply Chain Development and Management Theme

Many manufacturers have supplier selection and supplier approved processes in place, yet demands on speed to market often result in circumvention of these processes. It has also been found at supply agreements often conflict with the requirements of other agreements and drive the wrong behavior on both sides of the relationship. Additionally, although supplier qualification is not a new concept, it has been found that the elements of risk assessed are often not representative of key cross-functional requirements, and therefore, do not provide a complete representation of risk.

Xavier, Good Supply Practices Concept Paper, 2015

Infrastructure Modernization

How Reliable is the Facility and Process (whether in-house or CMO)?

- Inadequate manufacturing capability is a frequent cause of drug defects and critical drug supply shortfalls
  - For example, ISPE's industry survey cited lyophilization and sterile manufacturing as two areas in need of improvement.
- "Some…inspections have found operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized."

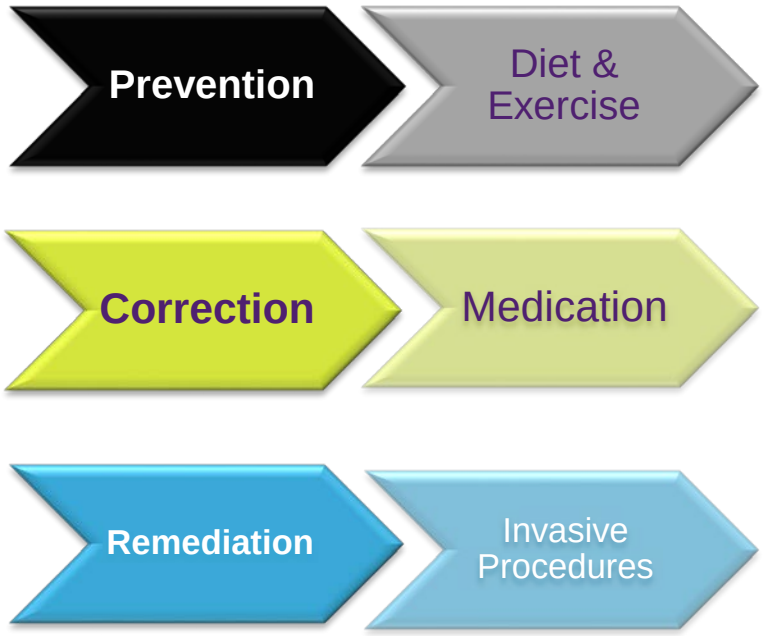
Janet Woodcock, M.D., CDER Center Director (December, 2013)

Manufacturing: Past and Present

20th Century Paradigm: Manually intensive operation versus

21st Century Paradigm: Manufacturing changes remove direct human-machine interaction.

How Do You Know If Your PQS is a Healthy One?



Z. Kauffman, FDA/EMA/PDMA /PDA/ISPE/JPMA ICH Q10 Training Conferences

Quality Culture: What halts or delays implementation of needed change/improvement?

Vision	+	Skills	+	Incentives	+	Resources	+	Action Plan	=	Change
		Skills	+	Incentives	+	Resources	+	Action Plan	=	**Confusion**
Vision			+	Incentives	+	Resources	+	Action Plan	=	**Anxiety**
Vision	+	Skills			+	Resources	+	Action Plan	=	**Resistance**
Vision	+	Skills	+	Incentives			+	Action Plan	=	**Frustration**
Vision	+	Skills	+	Incentives	+	Resources			=	**Treadmill**

Factors in managing complex change (Knoster, Villa, Thousand, 2000)

What is "Compliance?"

- *The degree of constancy and accuracy with which a patient follows a prescribed regimen, as distinguished from adherence or maintenance. (Medicine)*

  Q: What is the result of the failure to comply with taking a drug (e.g., antiseizure, heart failure, antibiotic) as directed?

  A: Remedy is likely **less effective**. Health outcome is **less predictable.**

- *The act or process of complying to a regimen. (Manufacturing)*

  Q: What happens if you do not follow the Proven Process, or the Pre-Defined Procedure? Is the result as robust?

  A: When the process/method proven to be **reliable** is not followed, the quality of the final output is **less certain.**

American Heritage Stedman Medical Dictionary and *Merriam Webster Dictionary*

NOTE:

– …The ill-effects of patient non-compliance with the prescribed dosing regime are pretty well understood in the medical community. So in this context we understand how important COMPLIANCE is.

– But what if you are not routinely complying with the manufacturing process and specifications that produced the originally approved S&E drug?

– IN EITHER CASE, YOU HAVE LESS CONFIDENCE OF A PREDICTABLE OUTCOME. (i.e., A safe and effective drug may not be available to the patient when the need it.)

Summary

- Senior management is responsible for assuring an effective Quality System
- Know your processes; know your business partners
- Quality Risk Management
  - Robust manufacturing design
  - Strong supplier management programs
  - Ongoing vigilance to assure predictable quality and supply, and identify areas needing improvement

"There is no longer such a thing as an American drug supply; there is a global drug supply…We know that, every day, some of those in the manufacturing and distribution chains for these products cut corners in small or large ways. They gain a competitive advantage or a monetary windfall from this non-compliance. But, they put our citizens at risk, and we cannot tolerate that."

– Former Commissioner Margaret Hamburg, Geneva, Switzerland (2011)

Office of Manufacturing Quality
FDA/CDER Office of Compliance

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm095412.htm

Email: rick.friedman@fda.hhs.gov

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